Trial Statistical Analysis Plan

c09146161-01

BI Trial No.:	1199. 202
Title:	The special drug use-results survey (All-Case Surveillance) of Ofev® Capsules in patients with Idiopathic Pulmonary Fibrosis (IPF) in Japan Including Protocol Amendment 4 <1199.202>-protocol-amendment-4 [include c03498541-04]
Investigational Product(s):	Nintedanib
Responsible trial statistician(s):	[redacted] Address: [redacted] Phone: [redacted], Fax: [redacted]
Date of statistical analysis plan:	14 JUN 2022 SIGNED
Version:	1

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2. LIST OF ABBREVIATIONS

Include a list of all abbreviations used in the TSAP

Term	Definition / description
ADR	Adverse Drug Reaction
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BSA	Body surface area
FEV_1	Forced Expiratory Volume in 1 second
FVC	Forced Vital Capacity
HOT	Home Oxygen Therapy
IIPs	Idiopathic Interstitial Pneumonias
IPF	Idiopathic Pulmonary Fibrosis
MedDRA	Medical Dictionary for Regulatory Activities
MMF	Mycophenolate Mofetil
MMRM	Mixed Effects Model for Repeated Measures
NIS	Non-interventional Study
OCS	Oral corticosteroid
PD	Protocol deviation
PT	Preferred term
Q1	Lower quartile
Q3	Upper quartile
RMP	Risk Management Plan
SAE	Serious Adverse Event
SD	Standard deviation
SMQ	Standardised MedDRA query
SOC	System organ class
TBILI	Total bilirubin
ToC	Table of contents
TSAP	Trial statistical analysis plan

3. INTRODUCTION

The purpose of this document is to provide a more technical and detailed elaboration of the principal features of the analysis described in the protocol, and to include detailed procedures for executing the statistical analysis of the post-marketing surveillance (PMS) data.

This TSAP assumes familiarity with the Non-interventional Study (NIS) Protocol, including Protocol Amendments. In particular, the TSAP is based on the planned analysis specification as written in NIS Protocol Section 9.7 “DATA ANALYSIS”. Therefore, TSAP readers may consult the NIS Protocol for more background information on the study, e.g., on study objectives, study design and population, treatments, definition of measurements and variables, planning of sample size.”

SAS® Version 9.4 or later will be used for all analyses.

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

Covariance matrix was changed from “compound symmetry” specified in NIS protocol to “unstructured” in MMRM (Mixed Effects Model for Repeated Measures) analysis.

Added the following events to priority survey items because they were added in Japanese RMP.

[redacted]

5. ENDPOINT(S)

5.1 PRIMARY ENDPOINT(S)

There is no primary endpoint for effectiveness, the primary objective of the PMS study is the evaluation of safety (see the NIS Protocol Section 10.3.2).

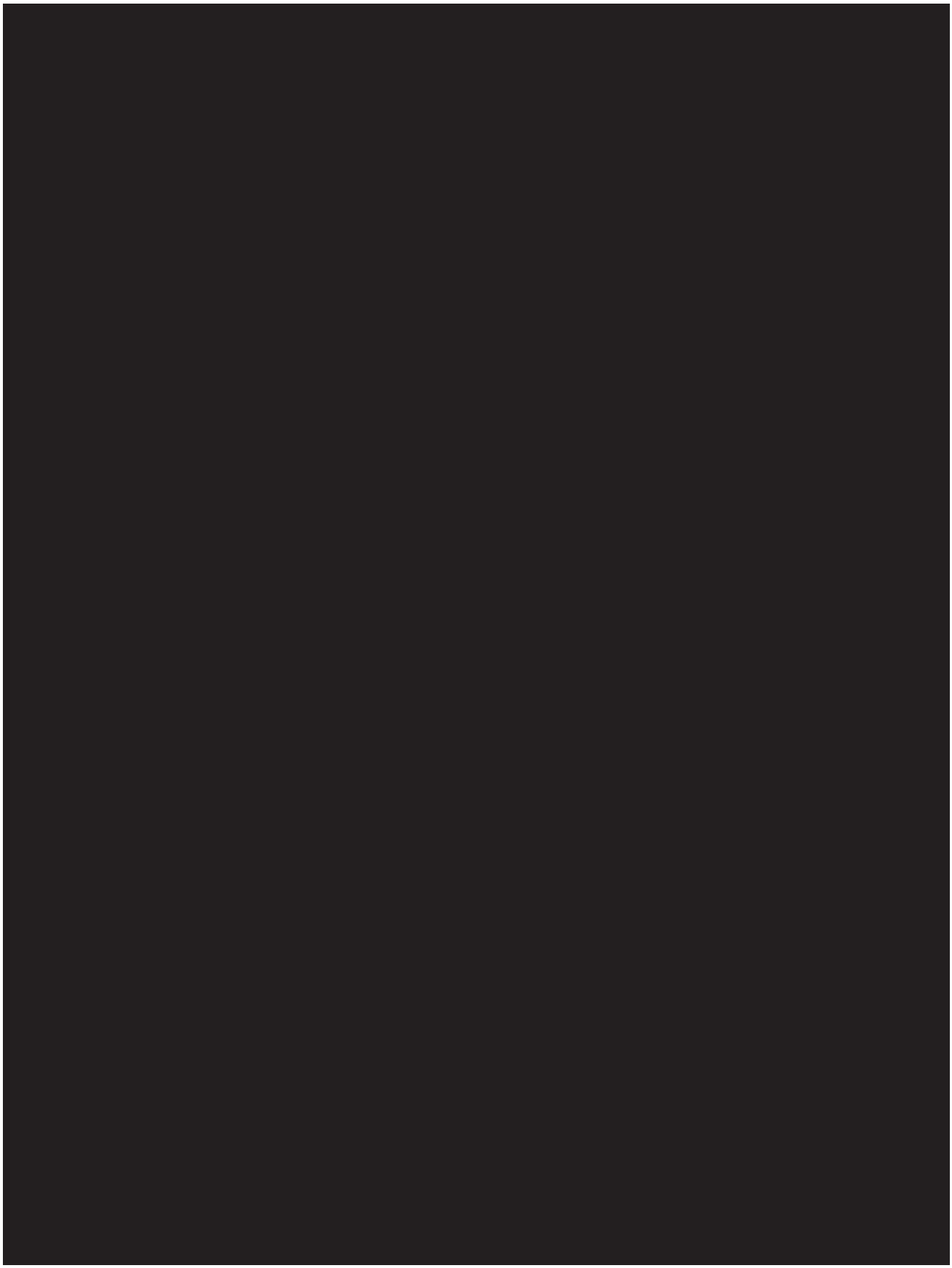
5.2 SECONDARY ENDPOINT(S)

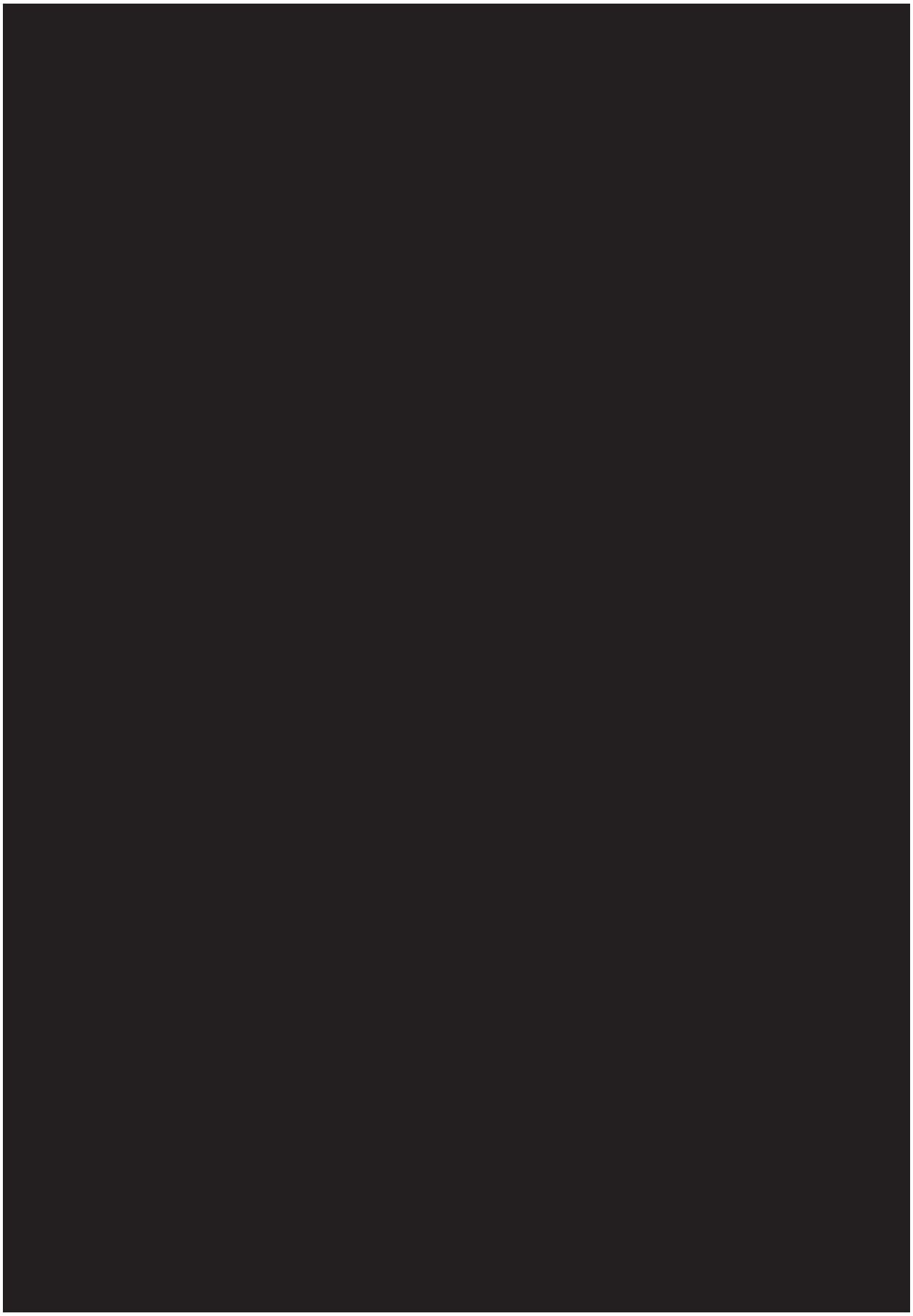
5.2.1 Key secondary endpoint(s)

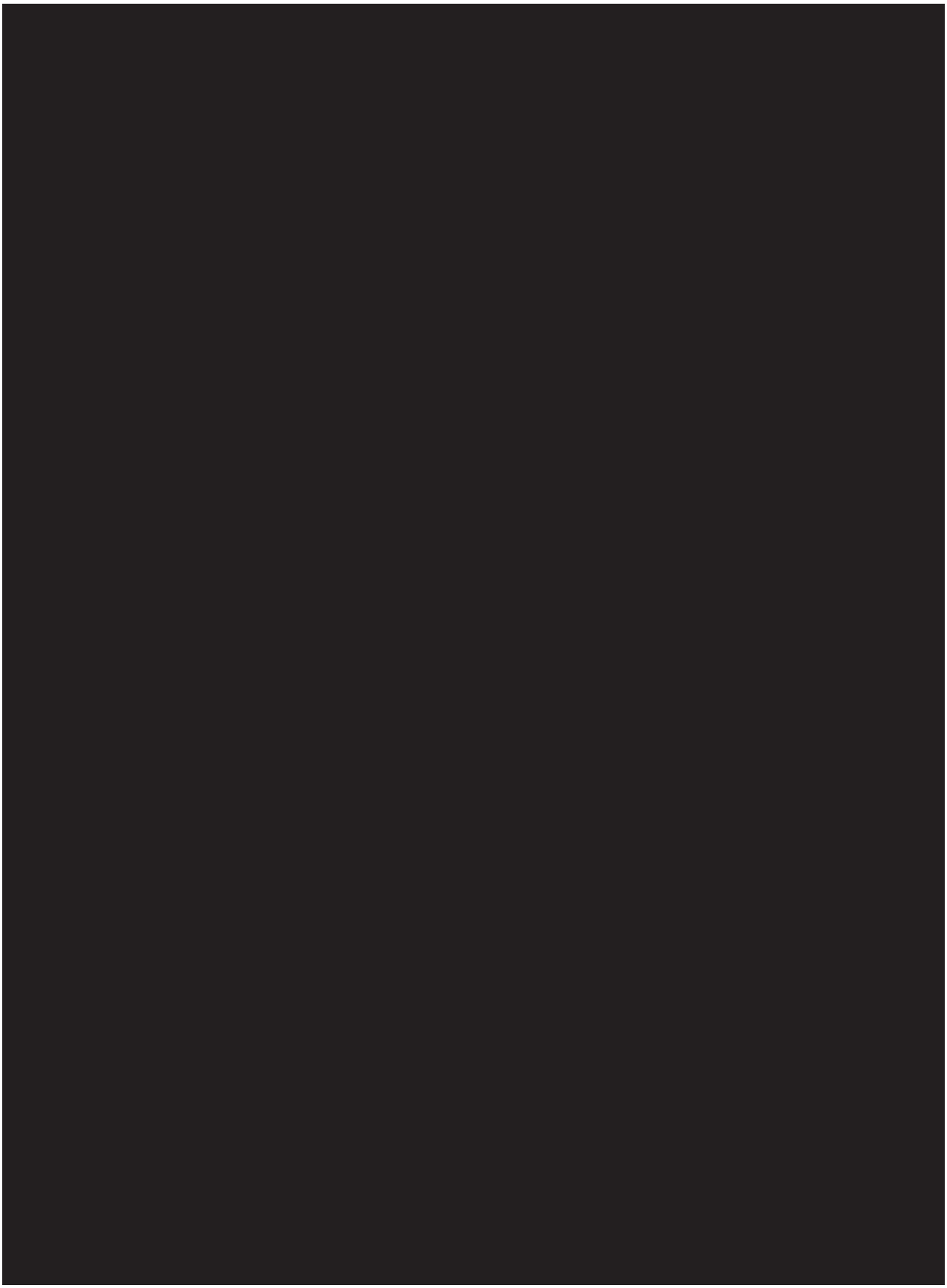
This section is not applicable as no key secondary endpoint has been specified in the NIS protocol.

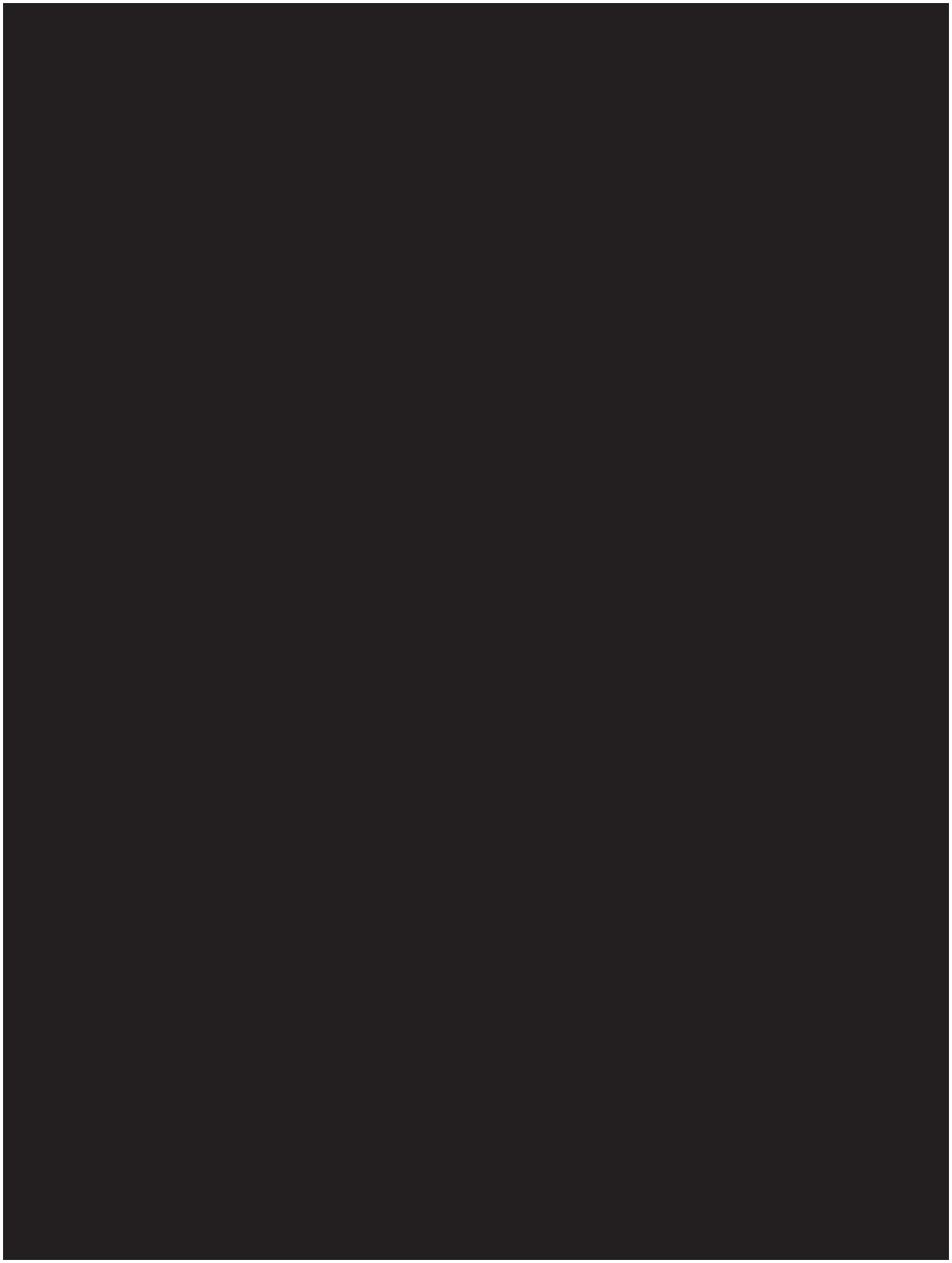
5.2.2 Secondary endpoint(s)

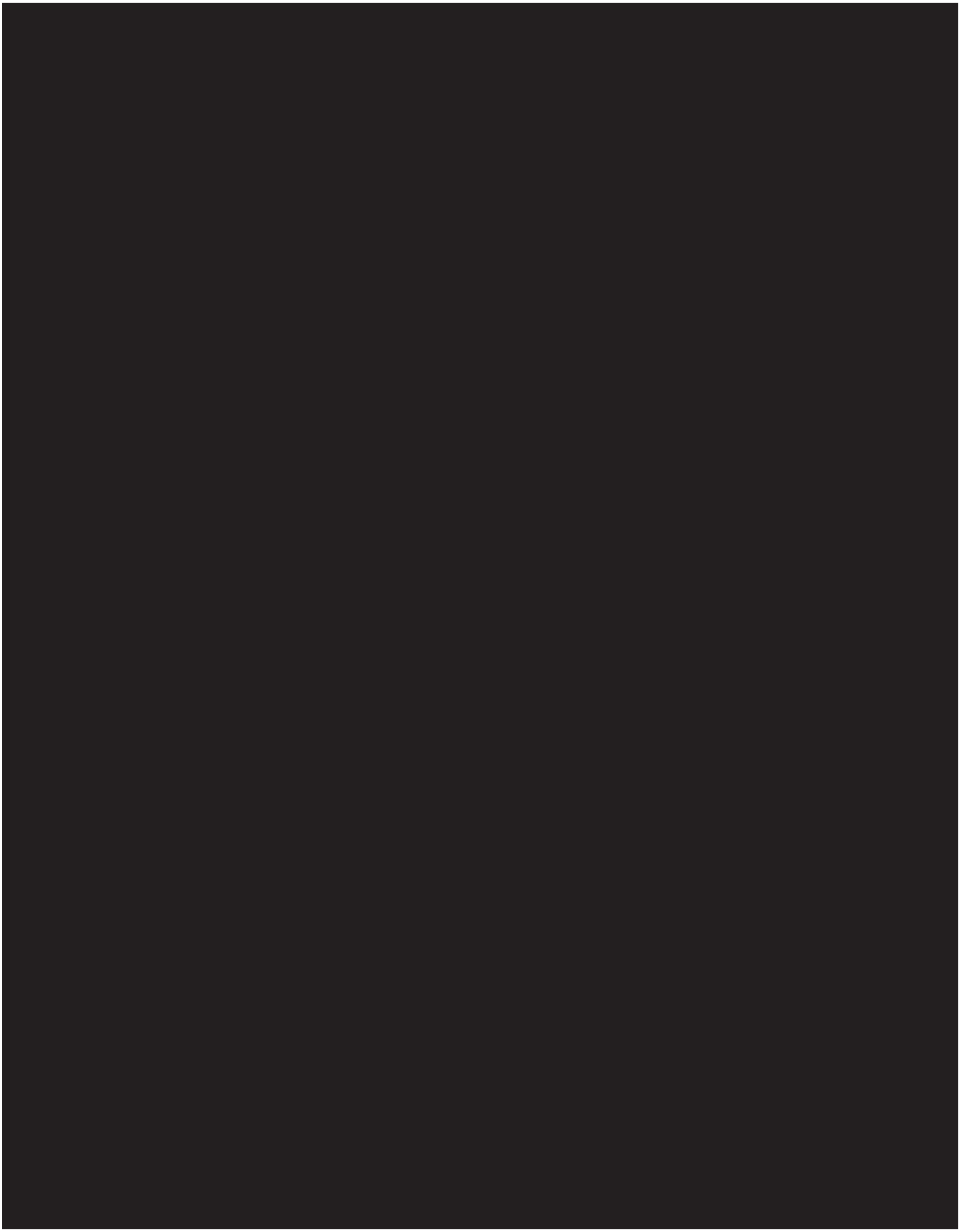
The secondary endpoints will be used as stated in the NIS Protocol Section 10.3.2.

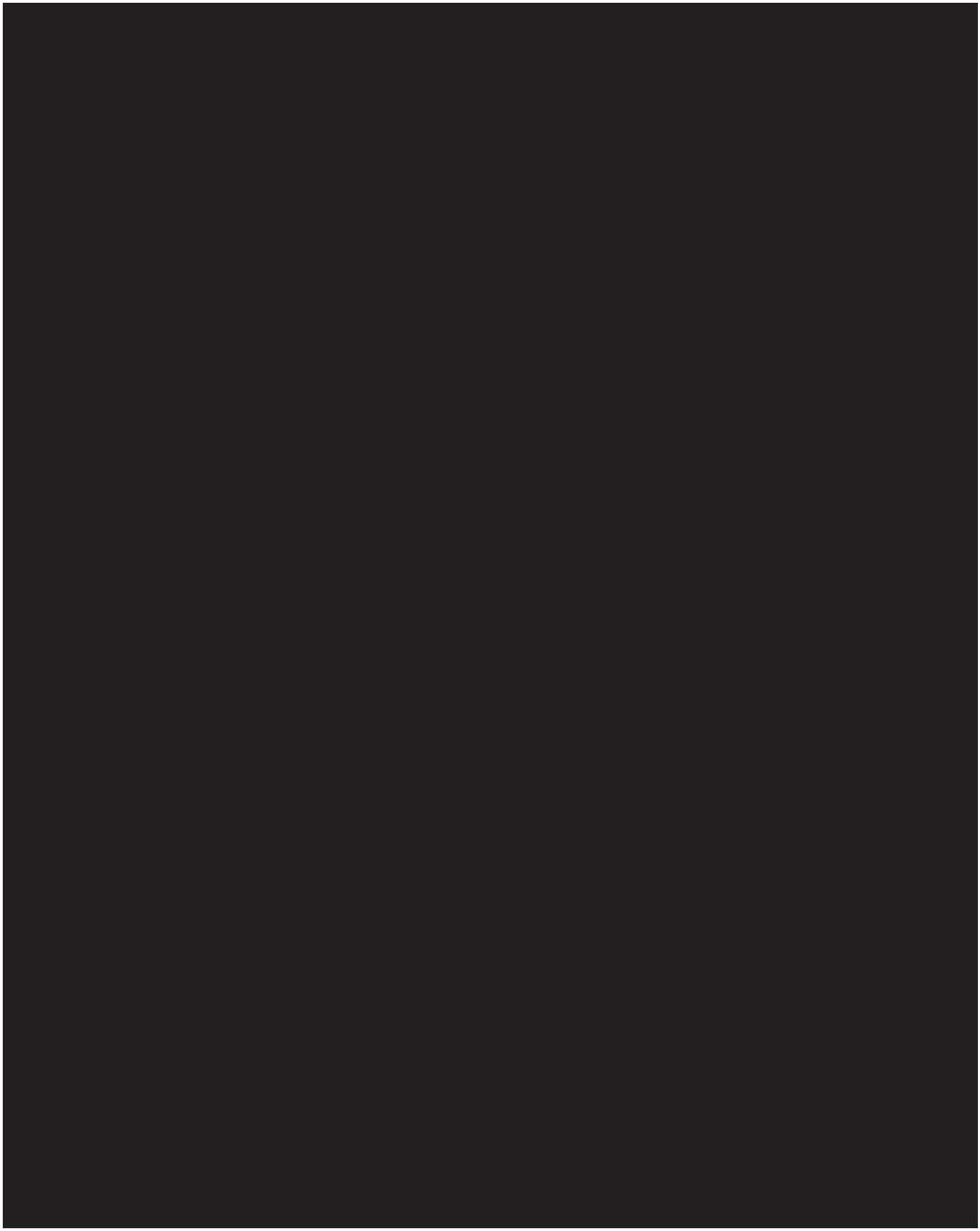












6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENT(S)

For basic study information on treatments, please refer to NIS Protocol Section 5. The technical specification for treatment set-up is described in the analysis data set (ADS) plan. For safety analyses, data up to 28 days after last treatment intake will be considered as on-treatment.

6.2 IMPORTANT PROTOCOL DEVIATIONS

Provide a table specifying the definition of all important PDs with columns for PD category / code, PD description, additional comment/example and a column to describe which PDs will be used to exclude patients from the different patient analysis sets. The final decision about which patients will be excluded from analysis sets will be taken during the course of the study and at report planning meetings before database lock at the latest.

Table 6.2: 1 Important protocol deviations

Category / Code		Description	Requirements	Method	Excluded from
A		**Entrance criteria not met**			
	A1	Patient of non-approved Indication	Non-IPF patient	Manual	Effectiveness
B		**Trial medication**			
	B1	No treatment with Ofev® Capsules		Automated	Safety/Effectiveness
C		**Missing data**			
	C1	No patient visit after registration	No visit made after the entry	Automated	Safety/Effectiveness
	C2	No safety observation was documented after registration	No AE occurrence information and details	Manual	Safety/Effectiveness
	C3	No FVC and FVC% value at baseline and/or at post treatment	None of value about FVC and FVC % predicted for effectiveness analysis, at baseline and/or at post treatment	Automated	Effectiveness (for FVC and %FVC analysis only)
	C4	No data reliability	No signature by contracted investigator in book1	Manual	Safety/Effectiveness
D		**Invalid registration**			
	D1	Required registration procedure was not followed	After the approval condition has been removed. See NIS protocol section 10.2.2.2.	Manual	Safety/Effectiveness
	D2	Patient started Ofev® Capsules treatment out of registration period	After the approval condition has been removed See NIS protocol section 10.2.2.2.	Automated	Safety/Effectiveness
E		**Contract**			
	E1	No valid site contract		Manual	All(registration)

6.3 SUBJECT SETS ANALYSED

The safety set will be the basis of all demographic, baseline and safety analyses.
Effectiveness analysis will be done on the basis of the effectiveness set.

- Safety set:
  This patient set includes all patients who didn't have any IPDs leading to exclusion from this analysis set as defined in Table 6.2: 1.

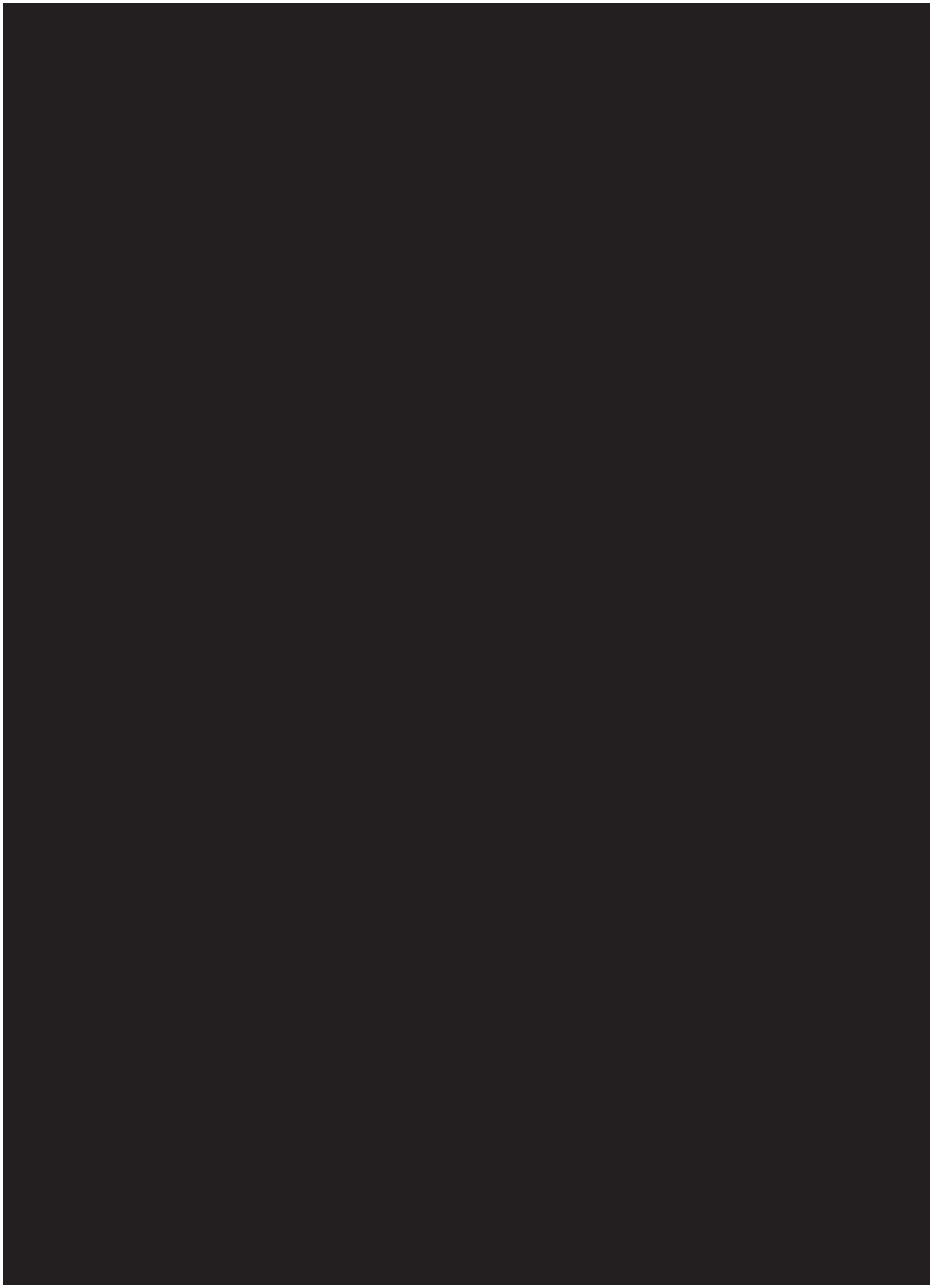
- Effectiveness set:
  This patient set includes all patients with Ofev® Capsules in the safety set who were suffering from the approved indication. Further IPDs leading to exclusion from this analysis set are defined in Table 6.2: 1.

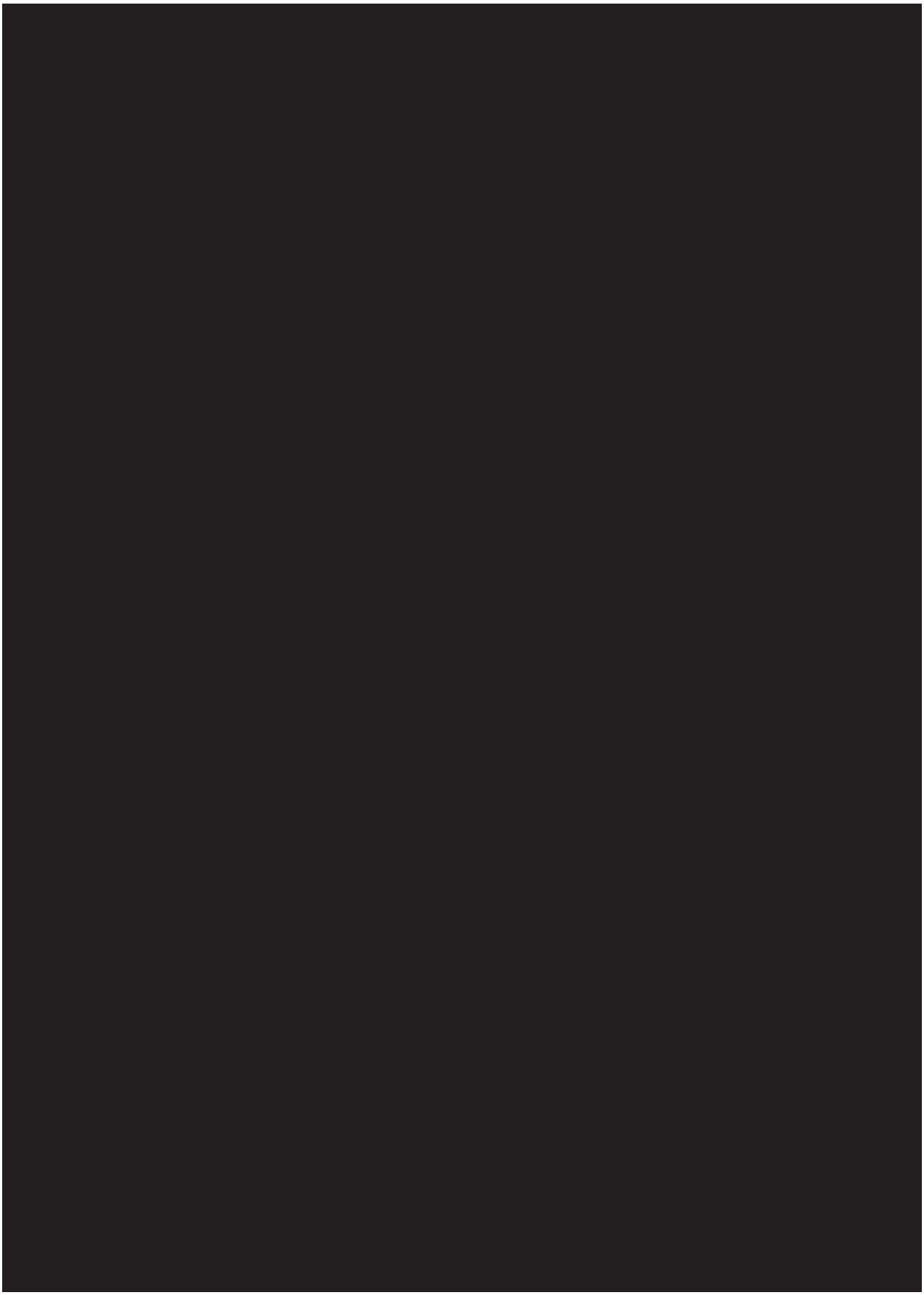
  In FVC and %FVC analysis, patients with FVC and %FVC value at baseline and post treatment in effectiveness set are used.

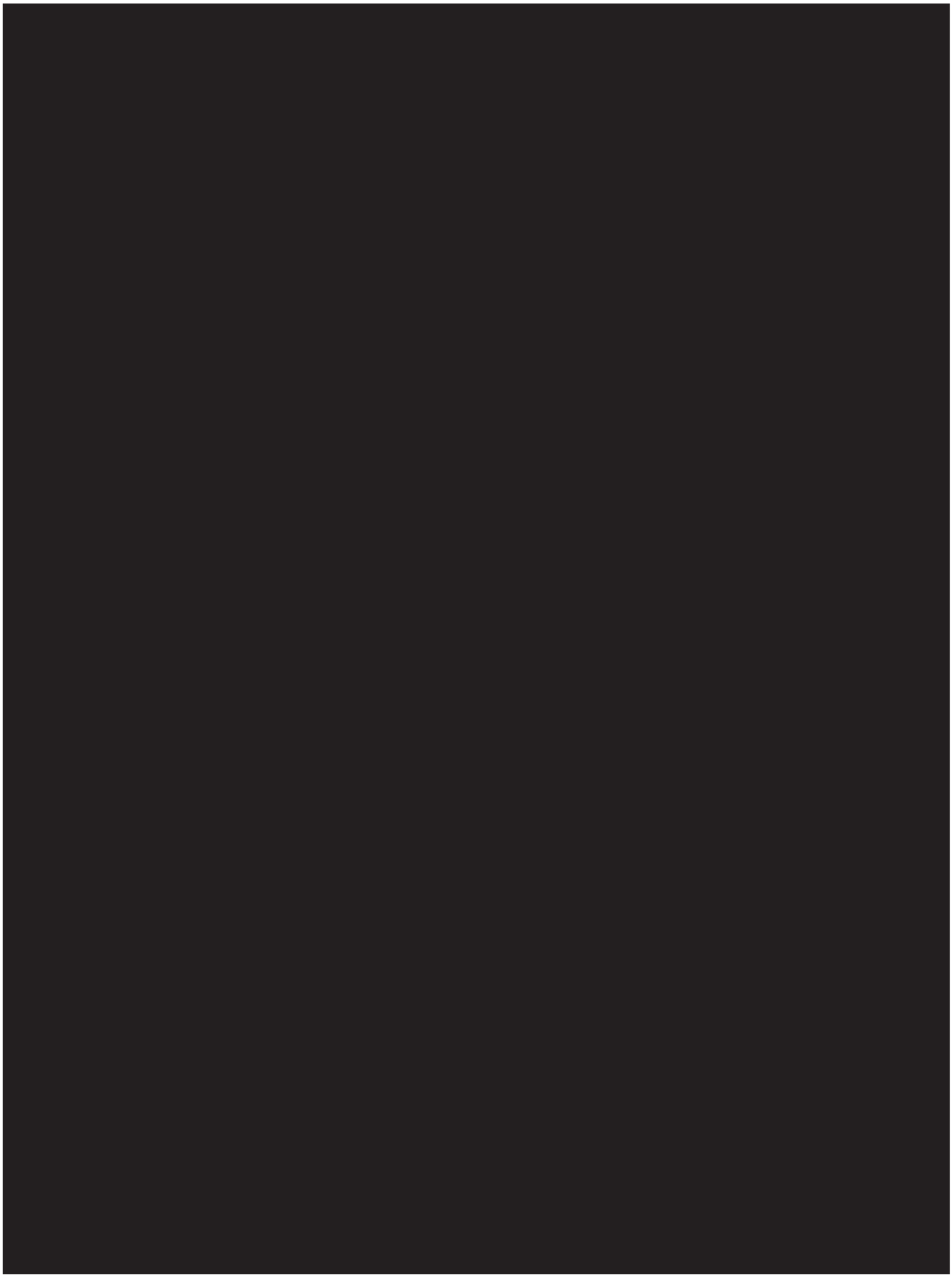
Table 6.3: 1 Subject sets analysed

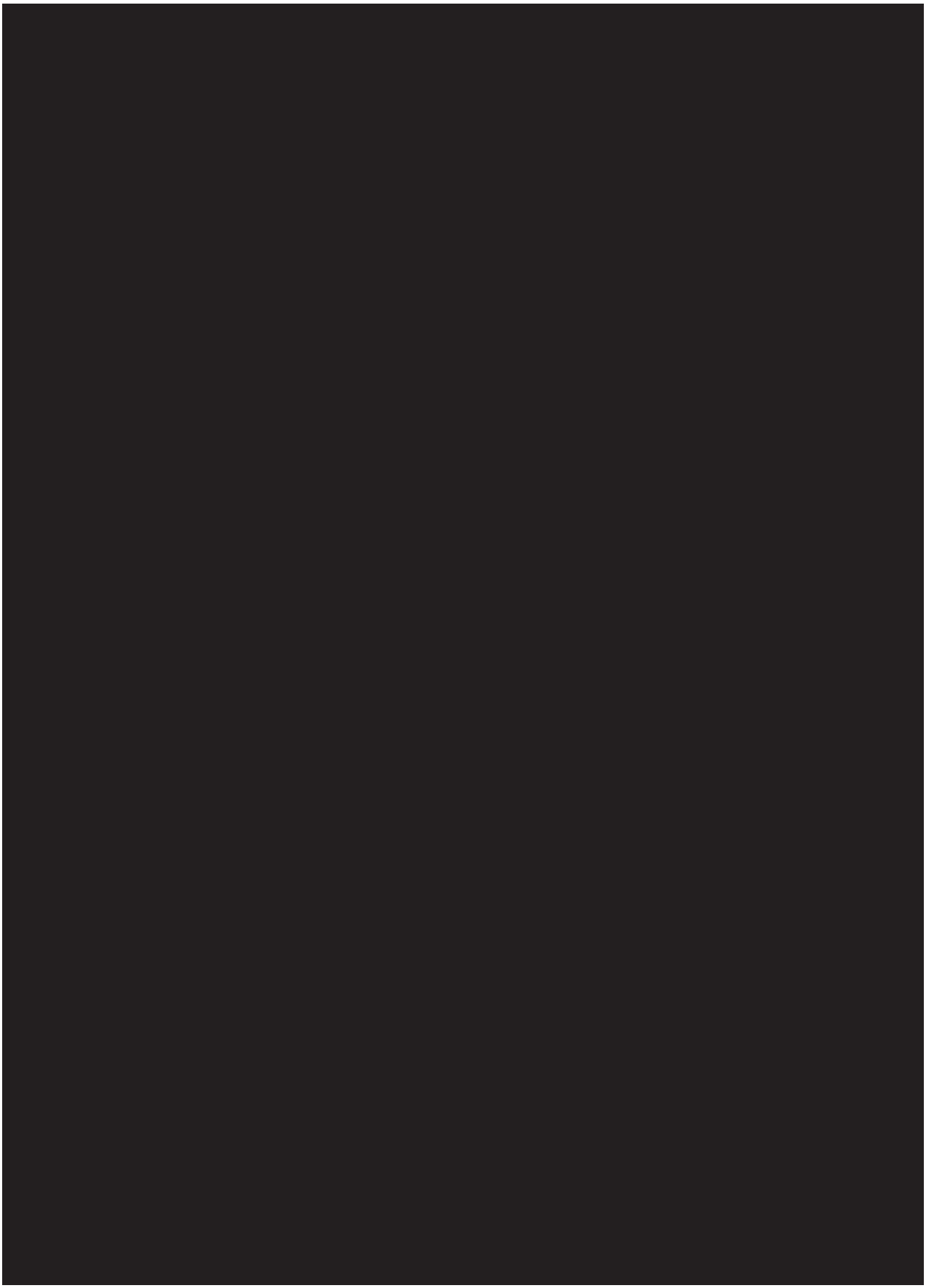
	Subject set	
Class of endpoint	Safety set	Effectiveness set
Primary endpoints	X	
(other) Secondary and further endpoints		X
Safety endpoints	X	
Treatment exposure	X	X
Demographic/baseline endpoints	X	

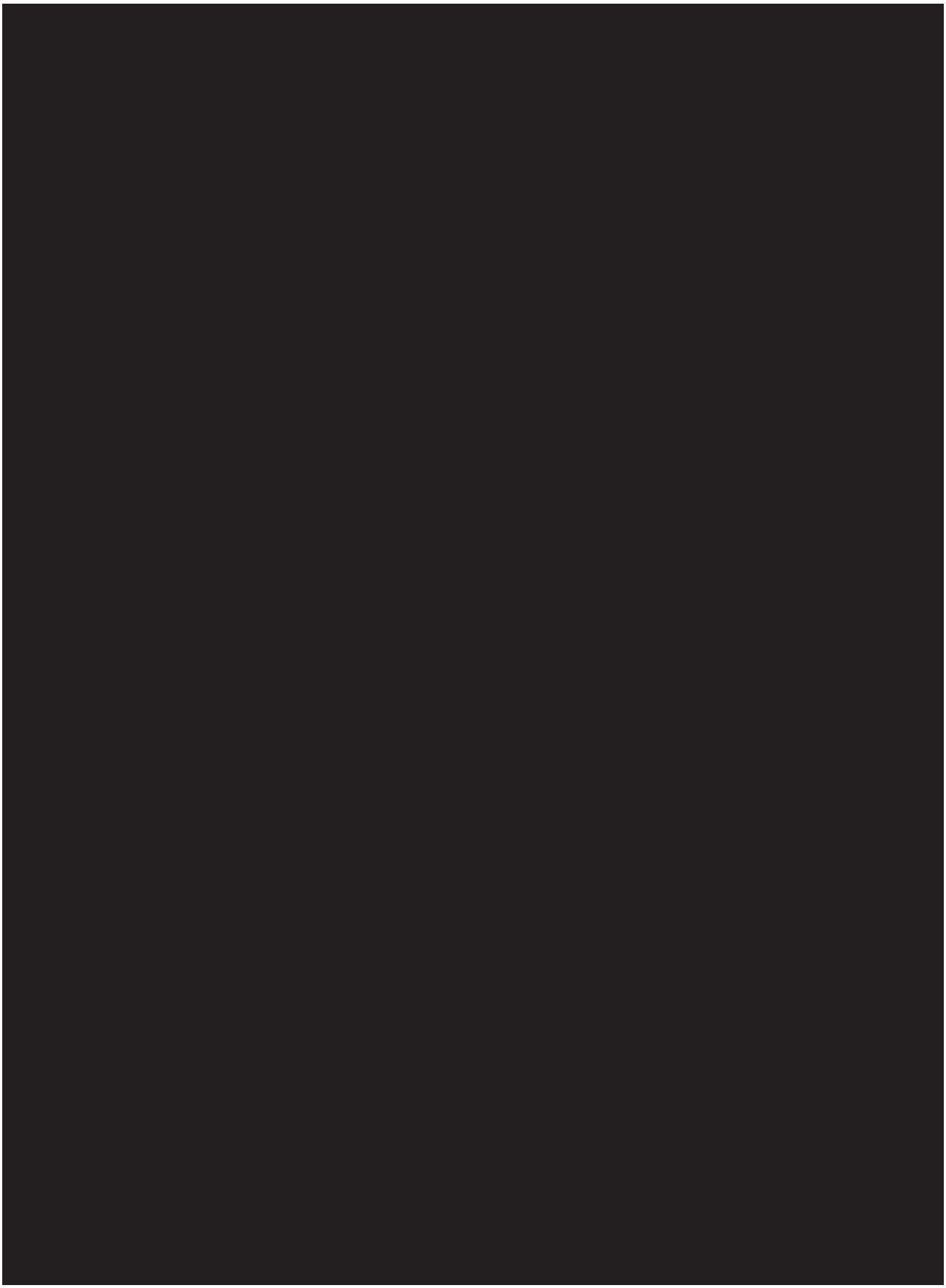
[redacted]

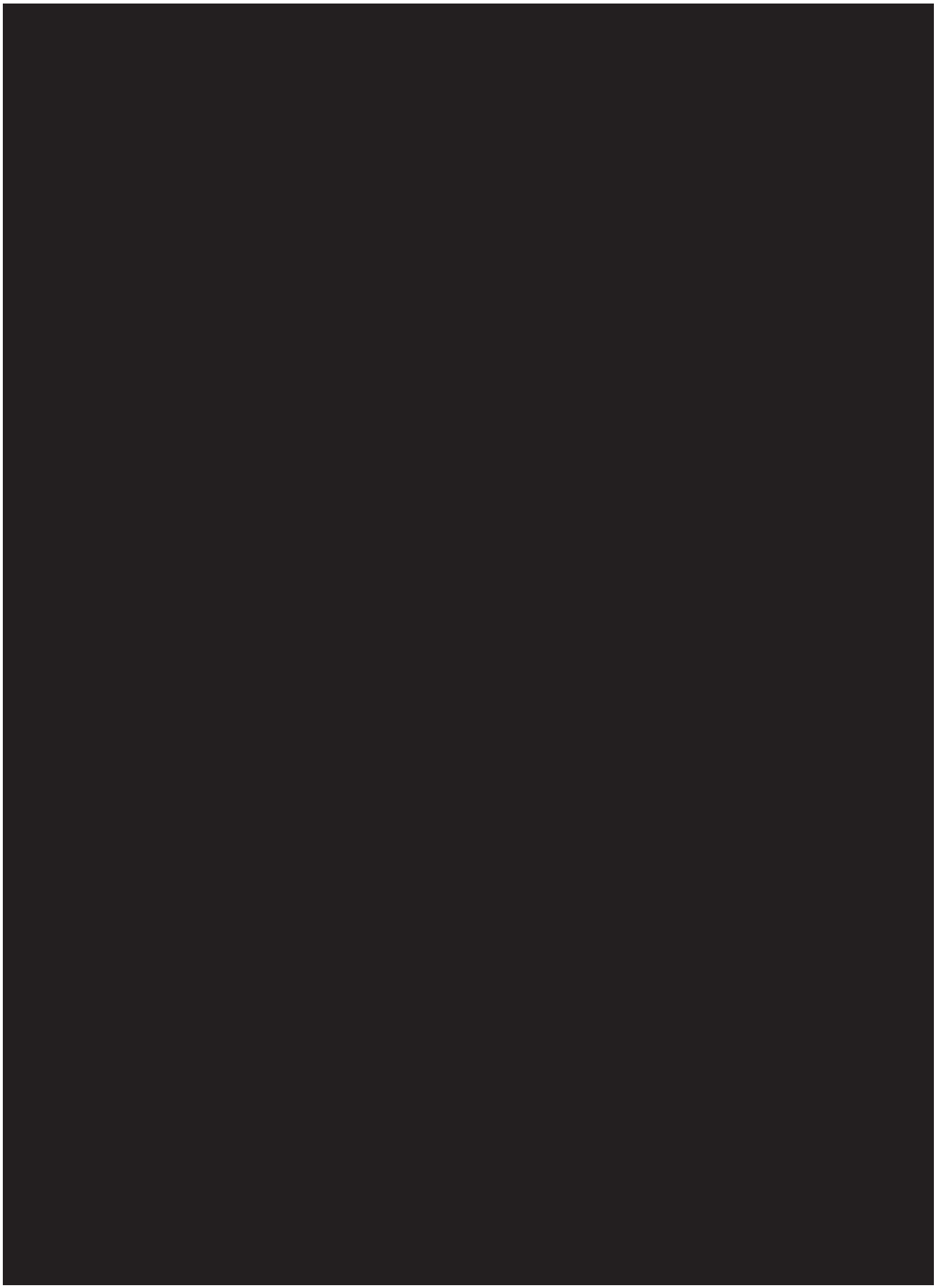












6.5 POOLING OF CENTRES

This section is not applicable because centre is not included in the statistical model.

6.6 HANDLING OF MISSING DATA AND OUTLIERS

Safety:

Missing or incomplete AE dates are imputed according to BI standards ((‘Handling of Missing and Incomplete AE Dates’ (1))).

Missing or partial date information other than AE and treatment dates will be replaced according to the following rules.

Effectiveness:

Missing effectiveness data will not be imputed.

Missing or partial date information will be replaced according to the following rules.

YEAR	MONTH	DAY	YMD	DT
“Unknown” (tick-box)			UNKNOWN	.
yyyy	Null or “Unknown”	Null	yyyy	yyyy/01/01
yyyy	mm	Null or “Unknown”	yyyymm	yyyy/mm/01

If the date of data which is collected after treatment of Ofev® Capsules in the CRF is before start of Ofev® Capsules, they will be set to missing.

Demographics:

Missing or partial date information in birth date will be replaced according to effectiveness rules.

Treatment exposure:

Date of last Ofev® Capsules intake:
To calculate duration of Ofev® Capsules treatment at an interim analysis, the date is imputed with the following date according to the book number.

Book1: the first treatment date + 365.25/12×3
Book2: the first treatment date +365
Book3: the first treatment date +365+(365.25/12×6)
Book4: the first treatment date +730 days.

Missing or partial date information will be replaced according to the following rules.

YEAR	MONTH	DAY	YMD	DT
yyyy	mm	Null or "Unknown"	yyyymm	yyyy/mm/the last day of the month
yyyy	mm	The beginning of the month	yyyymm	yyyy/mm/10
yyyy	mm	The middle of the month	yyyymm	yyyy/mm/20
yyyy	mm	The end of the month	yyyymm	yyyy/mm/ the last day of the month

Note that in general when tabulating AEs, and/or demographic and baseline characteristics variables reported as unknown will be treated as such; otherwise treated as missing data.

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

With regard to effectiveness and safety endpoints, the term "baseline" refers to the last observed measurement before administration of Ofev® Capsules. The first date of the administration of Ofev® Capsules is included in "baseline".
Effectiveness analyses will be performed based on calculated visits as shown in Table 6.7: 1. If two or more data points of a patient fall into the same interval, the closest value to the planned day will be selected. If there are two observations which have the same difference in days to the planned day or if there are two observations on the same day, the first value will be used.

Table 6.7: 1 Baseline, time windows and calculated visits

		Time window (actual days on treatment)	
Week label	Planned days	Start	End
Baseline	1	The last observed measurement before administration of Ofev® Capsules	
Week 4	28	2	59
Week 13	91	60	136
Week 26	182	137	227
Week 39	273	228	318
Week 52	364	319	409
Week 65	455	410	500
Week 78	546	501	591
Week 91	637	592	682
Week 104	728	683	End of study

7. PLANNED ANALYSIS

For End-Of-Text (EoT) tables, the set of summary statistics is: N / Mean / SD / Min / Q1/ Median / Q3 / Max.

Tabulations of frequencies for categorical data will include all possible categories and will display the number of observations in a category as well as the percentage (%) relative to the respective treatment group (unless otherwise specified, all patients in the respective patient set whether they have non-missing values or not). Percentages will be rounded to two decimal places. The category missing will be displayed only if there are actually missing values.

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Only descriptive statistics are planned for this section of the report.

7.2 CONCOMITANT DISEASES AND MEDICATION

Concomitant diseases will be coded by the latest version of Medical Dictionary for Regulatory Activities (MedDRA). Only descriptive statistics are planned for concomitant diseases. Concomitant medication will be coded by latest version of “Nihon-iyakuhinshu”.

7.3 TREATMENT COMPLIANCE

It is not planned to analyse treatment compliance.

7.4 PRIMARY ENDPOINT(S)

There is no primary endpoint for effectiveness as the primary objective of the PMS study is the evaluation of safety.

7.4.1 Primary analysis of the primary endpoint(s)

The analysis will be performed as defined in the NIS Protocol (see the NIS Protocol Section

7.3.1).

7.4.2 Sensitivity analysis, subgroup analysis, exploratory analysis of the primary endpoint(s)

The subgroup analysis for the frequency of patients with adverse drug reactions (ADRs) will be performed (see Section 6.4).

7.5 SECONDARY ENDPOINT(S)

7.5.1 Key secondary endpoint(s)

7.5.1.1 Primary analysis of the key secondary endpoint(s)

This section is not applicable as no key secondary endpoint has been specified in the NIS protocol.

7.5.1.2 Sensitivity analysis, subgroup analysis, exploratory analysis of the key secondary endpoint(s)

This section is not applicable as no key secondary endpoint has been specified in the NIS protocol.

7.5.2 (Other) Secondary endpoint(s)

For the absolute change from baseline in FVC [mL] at Week 104, descriptive statistics will be calculated. A 95% confidence interval for the mean change from baseline will also be calculated. In addition to the descriptive evaluation, the absolute change from baseline in FVC [mL] will be analysed using a mixed effects model for repeated measures (MMRM) approach.

MMRM analysis will includes all the available longitudinal observations at each post baseline visit during the treatment period. The statistical model includes baseline value as covariate, visit, gender, baseline age, baseline height, baseline FVC (or FVC% pred) and baseline FVC (or FVC% pred)-by -visit as fixed effect, and patients as random effect. The differences from baseline for each visit by patient are assumed to have a particular variance-covariance structure which is “unstructured”. The SAS procedure MIXED will be used involving the restricted maximum likelihood estimation and the Kenward and Roger approximation of denominator degrees of freedom. Subsequently, LS means are computed at every time point and their respective standard error and 95% confidence interval estimate account for the estimated covariance parameters.

7.7 EXTENT OF EXPOSURE

Only descriptive statistics are planned for this section of the report.

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the safety set.

7.8.1 Adverse events

Unless otherwise specified, the analyses of adverse events (AEs) will be descriptive in nature. All analyses of AEs will be based on the number of patients with AEs and NOT on the number of AEs.

Furthermore, for analysis of AE attributes such as duration, severity, etc. multiple AE occurrence data on the CRF, will be collapsed into AE episodes provided that all of the following applies:

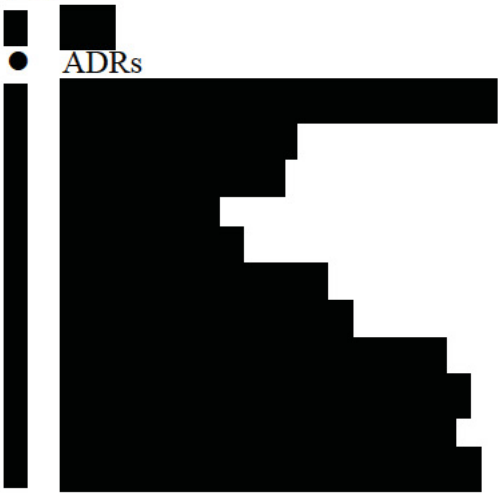
- The same MedDRA lowest level term was reported for the occurrences
- The occurrences were time-overlapping or time-adjacent (time-adjacency of 2 occurrences is given if the second occurrence started on the same day or on the day after the end of the first occurrence)
- Treatment did not change between the onset of the occurrences OR treatment changed between the onset of the occurrences, but no deterioration was observed for the later occurrence

For further details on summarization of AE data, please refer to BI standards ('Analysis and Presentation of Adverse Event Data from Clinical Trials' (2))

AE analyses will be carried out after integrating AE data from CRF and AE data from Local PV safety database (Perceive).
In addition, events coded as "no adverse event", etc. will not be included in the AE analyses. The list of codes will be provided by Drug Safety.

The frequency of patients with the following items will be summarized by primary SOC and PT.

- [redacted]
- ADRs
- [redacted]



An ADR is defined as an AE for which either the investigator or the sponsor (or both) assess the causal relationship to Ofev® Capsules either as "Yes "or "Unknown". A serious AE is defined as an AE for which either the investigator or the sponsor (or both) assess the seriousness as "Serious".
The SOCs will be sorted according to the standard sort order specified by European Medicines Agency, PTs will be sorted by frequency (within SOC).

[redacted] will also be reported by intensity.
The frequency of patients having hepatic dysfunction at baseline with [redacted] will be summarized. Patients with [redacted] will be summarized by IIPs severity grade

[redacted]

To compare the risk of experiencing at least one ADR, [redacted] in different patient subgroups, frequency tabulation stratified by different patient subgroups will be provided with odds ratios and exact 95% confidence intervals whenever specified (see Section 6.4). Logistic regression models will be used and odds ratios together with 95% confidence intervals will be provided.

Frequency tabulation of [redacted] stratified by different patient subgroups (the following items) will be provided with odds ratios and exact 95% confidence intervals whenever specified. Logistic regression will be used for odds ratio.
[redacted]

Frequency tabulation of [redacted] stratified by different patient subgroups (the following item) will be provided with odds ratios and exact 95% confidence intervals whenever specified. Logistic regression will be used for odds ratio.
[redacted]

Frequency tabulation of [redacted] stratified by different patient subgroups (the following concomitant medications) will be provided with odds ratios and exact 95% confidence intervals whenever specified. Logistic regression will be used for odds ratio.

[redacted]

In addition, summaries for the time to onset of first episode for the ADRs will be tabulated, by duration (<=31, >31 to 91, >91 to 182, >182 to 273, >273 to 364, >364 to 455, >455 to 546, >546 to 637, >637 to 728, >728 [days]), by primary SOC, and PT.

The time to onset of the first adverse drug reaction categorized into priority survey items and diarrhoea will be tabulated by the time(0 to 14, 15 to 30, 31 to 60, 61 to 90, 91 to 180, 181 to 270, 271 to 360, 361 to 540, 541 to 727, =>728 [days]) and summarised.

Incidence rate of [redacted], ADRs and [redacted] will be summarized by person-year method, too. Pearson-year is defined as:

- if the patient has the event: date of onset of the first event – date of first administration of Ofev® + 1 day
- if the patient did not have the event: date of last administration of Ofev® - date of first administration of Ofev® + 1 day

[redacted]

Kaplan-Meier plots including the number at risk will be prepared for [redacted]

7.8.2 Laboratory data

Only clinically relevant findings reported as AE will be analysed as a part of AE analyses.

7.8.3 Vital signs

Only clinically relevant findings reported as AE will be analysed as a part of AE analyses.

7.8.4 ECG

Only clinically relevant findings reported as AE will be analysed as a part of AE analyses.

7.8.5 Others

No plan for other safety parameters.

8. TIMEPOINT OF RELEASE OF TREATMENT INFORMATION

The treatment information will be loaded into the trial database at trial initiation.

9. REFERENCES

1	*BI-KMED-BDS-HTG-0035:* "Handling of missing and incomplete AE dates", current version; KMED.
2	*BI-KMED-BDS-HTG-0041*: "Analysis and Presentation of Adverse Event Data from Clinical Trials", current version; KMED.

11. HISTORY TABLE

Table 11: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
1	**14-JUN-22**	[redacted]	None	This is the final TSAP without any modification